REMARKS

Amendment of the claim

Claim 7 is amended for formal completeness and to avoid potential printing errors. The amendment is supported by the disclosure as filed, and in particular by the original claims.

Administrative matter

Applicant notes that the Office action refers to a rejection of claim 1. However, the sole claim pending after entry of the Examiner's Amendment entered in the Notice of Allowability mailed on 10 March 2004 is claim 7. Applicant understands that the renumbering of the claim for issue does not have effect in view of the Request for Continued Examination (RCE) in this application. Accordingly, the following remarks refer to the "prosecution numbering" of the claim.

Rejection under 35 U.S.C. § 103

The examiner rejects claim 7 on a single ground under § 103 based on Maloney *et al.* (*Blood*, 1995) in view of one of Press *et al.* (*Lancet*, 1995), Kaminsky *et al.* (*J. Clin. Oncol.*, 1996) ("1996"), or Kaminsky (U.S. Patent No. 6,287,537) ("'537"); further in view of Wahl *et al.* (ASCO abstract, 1998). Applicant respectfully traverses the rejection.

Claim 7

The claim is directed to a method of treating a subject having a CD-20$^+$ B-cell lymphoma in a subject that is refractory to treatment with unlabeled rituximab. The examiner construes "refractory" to mean either "resistant to treatment" or "relapsed." Applicant submits that this construction is overbroad.

While, as the examiner observes, there is no express definition of "refractory" in the specification, the intended sense of the term is found in the paragraph beginning at page 3, line 15, which specifies that "refractory" patients include those who "ha[ve] not exhibited appreciable tumor remission or regression after administration of a chimeric anti-CD20

antibody." The specification contrasts such patients with those who have relapsed, as discussed in the immediately preceding paragraph that begins at page 3, line 2.

The examiner's construction conflicts with both the ordinary meaning of "refractory" and the usage of the term in the art. "Refractory" ordinarily connotes obstinance, nonresponsiveness, or resistance. This concept differs from "relapsed," which in this context connotes a fallback from a therapeutic benefit obtained through an earlier therapy. Moreover, a patient that has relapsed following treatment with a given agent is not necessarily refractory to further treatment with that agent. The Wahl ASCO abstract cited by the examiner, for example, discloses that some patients that have relapsed following treatment with [^{131}I]-anti-B1 respond to (*i.e.*, are not refractory to) re-treatment with the same radiotherapeutic agent.

None of the references the examiner relies upon describes or suggests treating a patient with an antibody specific for the same antigen as an antibody to which the patient has become refractory, as that term is properly understood. Thus, the references fail to define the patient population required by the claim, and accordingly, they do not provide evidence of motivation to practice the claimed invention.

Maloney

Maloney reports the treatment of certain lymphoma patients with a single course of rituximab. The examiner correctly observes that some of the patients in the trial appeared not to respond to the therapy. All such patients, however, were naïve to treatment with anti-CD20 antibodies, and all received only one course of rituximab. Thus, no patients who were found to be refractory to anti-CD20 therapy were treated with any antibody. Moreover, the authors do not contemplate or discuss any future use of a radiolabeled antibody in the patient population represented in the trial for any purpose.

Press, Kaminsky 1996, and Kaminsky '537

Each of the secondary references cited by the examiner describes therapy using [^{131}I]-anti-B1. Applicant's invention does not reside in the use of a radioiodinated anti-CD20 antibody. Instead, claim 7 patentably defines over the prior art at least because of the particular population of patients (*i.e.*, rituximab-refractory CD20^{+} lymphoma patients) that it specifies.

None of the references teaches or suggests that [^{131}I]-anti-B1 would be useful to treat patients who are refractory to any anti-CD20 antibody, let alone refractory to rituximab.

The examiner relies particularly on Kaminsky '537, suggesting that it teaches that "in those cases that the tumors do not respon[d] to antibody B1 alone ... a response occurs only after a[ ] radiation dose of 131-I labeled B1." Office action at 5, second full paragraph. Applicant submits that the examiner is extrapolating teachings from the reference that it does not in fact support.

To support the assertion that Kaminsky '537 teaches the use of [^{131}I]-anti-B1 to treat patients who do not respond to unlabeled B1, the examiner cites the passage at col. 21, lines 47-53. This passage appears in a discussion of the modes of action that Kaminsky *et al.* believe to be operating in the clinical trial they describe as Example I. To explain why some patients in the trial were treated with a large dose of unlabeled anti-B1 before [^{131}I]-anti-B1 radioimmunotherapy (RIT), Kaminsky *et al.* teach at col. 21, lines 13-18, that it is their

> hypothesis that unlabeled antibody predosing may help radiolabeled antibody to bypass an antigenic sink (such as the spleen) and allow its better access to tumor sites through competitive binding mechanisms between unlabeled and labeled antibody.

The specification goes on to discuss several antitumor activities that unlabeled anti-B1 exhibits *in vitro* and *in vivo*. Kaminsky *et al.* suggest that the unlabeled antibody administered to saturate the hypothesized "antigenic sink" exerted therapeutic benefit in their clinical trial. In the portion that includes the sentence the examiner cites, the same paragraph continues at col. 21, lines 45-54:

> Indeed, in two of three instances in which a response occurred during tracer studies, the response was only seen after the largest dose of antibody (700 mg) was administered .... However, in those cases and those in which a response appeared to occur only after an RIT dose, a targeted radiation effect is also likely, especially since targeting of radioisotope was found to be so high in these cases in could result in the delivery to tumor of up to 120 cGy per tracer dose ... .

The discussion of Example I concludes at col. 21, lines 55-62, with a catalog of all of the immunological and radiological mechanisms that might contribute to the observed therapeutic effect, "in concert either additively or synergistically."

Considered in the context of the example from which it is drawn, the passage cited by the examiner does not support the conclusion that unlabeled anti-B1 is necessarily without therapeutic effect in the treated patients. Indeed, the observation that administration of unlabeled anti-B1 did not lead to an observed response prior to administration of [^{131}I]-anti-B1 is qualified: the example states that "a response *appeared* to occur only after an RIT dose" (emphasis added). Thus, Kaminsky *et al.* do not rule out a therapeutic benefit due to the unlabeled antibody. In other words, the patients who failed to respond observably to a "saturating" dose of unlabeled anti-B1 were not inherently refractory to that antibody, according to the concept of inherency as it is understood in the patent law. When a reference is silent about the presence or absence of a given feature in an embodiment it describes, the mere possibility (or even probability) that the feature might be present is insufficient to establish that it is inherently present. *See generally In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (C.C.P.A. 1981).

Kaminsky '537 does not expressly or objectively teach that [^{131}I]-anti-B1 should be used to treat patients that are refractory to unlabeled anti-B1. The specification teaches that several immunological mechanisms are *likely* to be operative in the combination therapy (*i.e.*, unlabeled + labeled anti-B1) that it describes. Indeed, if the hypothesis advocated at col. 21, lines 13-18, is correct, RIT with [^{131}I]-anti-B1 would not be effective without a preliminary dose of unlabeled anti-B1 to saturate the "antigenic sink." Thus, the evidence favors the conclusion that the patients described in Example I of Kaminsky '537 are not refractory to therapy with unlabeled anti-B1, and that Kaminsky *et al.* did not believe that they were so.

Wahl

The Wahl abstract establishes only that therapeutic levels of [^{131}I]-anti-B1 do not induce HAMA or other responses that would preclude successive courses of [^{131}I]-anti-B1 therapy. The reference does not describe or suggest the use of radioimmunotherapy after treatment with any unlabeled antibody, and it does not identify any patients that are refractory to unlabeled anti-B1. The abstract does indicate that one of the thirteen patients in the trial group failed to respond to a previous course of [^{131}I]-anti-B1 therapy, but it fails to report whether this patient did or did not respond to re-treatment with the same agent. Thus, it cannot be concluded whether this patient

might represent a case of a therapeutic response to RIT in a patient that had previously been refractory to the same treatment.

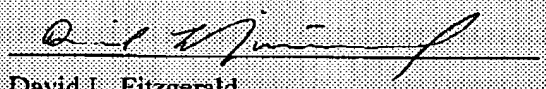
Discussion

As noted above, none of the references teaches or suggests that a radioiodinated murine anti-CD20 antibody should be used, or would be effective to treat patients that are refractory to any unlabeled anti-CD20 antibody. The examiner has identified some of the elements required by the invention of claim 7. However, no evidence in the cited prior art supplies motivation to identify or select the specific population of patients refractory to rituximab therapy for the prior art treatment utilizing [^{131}I]-anti-B1, as described by the secondary references. Absent evidence of motivation to combine the references in a manner that would yield the claimed invention, the examiner has failed to set forth a *prima facie* case of obviousness. *In re Rouffet*, 149 F.3d 1350, 1357; 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Accordingly, applicant requests that the examiner withdraw the rejection.

Conclusion

Applicant believes that this reply fully responds to the outstanding Office action. Reconsideration and allowance of the pending claim are respectfully requested. Should the examiner have any concerns, she is invited to contact the undersigned.

Respectfully submitted,



David L. Fitzgerald
Registration No. 47,347
Attorney for Applicant

SIDLEY AUSTIN BROWN & WOOD LLP
1501 K Street, N.W.
Washington, DC 2005
(202) 736-8818

9 February 2005